RECOGNIZING TB IN CHILDREN

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OBJECTIVES

- UNDERSTAND THE EPIDEMIOLOGY OF TB IN CHILDREN
- IDENTIFY CHILDREN IN HIGH-RISK GROUPS FOR TB
- DESCRIBE THE SIGNS AND SYMPTOMS OF ACTIVE TB IN CHILDREN
- RECOGNIZE THE DIAGNOSTIC TOOLS FOR TB IN CHILDREN

CHILDHOOD TB: GLOBAL BURDEN NOT FULLY KNOWN

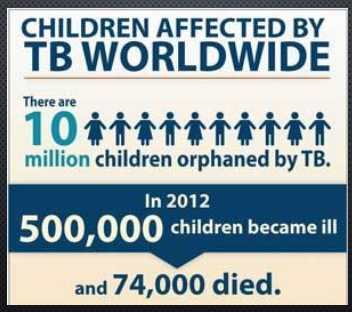
Range: 6-11% (~0.5- 1 million cases/year)

WHO 2012 estimate: 530,000 (6%)

Mathematical Modelling studies suggest: 650,000- 1,000,000

http://www.cdc.gov/tb/topic/populations/TBinChildren/global.htm
WHO 2013. Global TB Report

CHILDHOOD TB: GLOBAL BURDEN NOT FULLY KNOWN



* Excluding HIV/TB deaths

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WHO 2013. Global TB Report

CHILDHOOD TB IN THE UNITED STATES

DEFINITIONS, EPIDEMIOLOGY & HIGH RISK GROUPS

US PERSPECTIVE: CASE DEFINITIONS

- Incident cases among children <15 years of age
- Case verification categories:
  1) Laboratory confirmed cases
     - Positive culture or NAAT
     - Positive AFB smear when culture not attainable
  2) Clinical case definition
     - Positive TST or IGRA
     - Signs and symptoms of TB disease
     - Current treatment for TB disease
     - Completed diagnostic evaluation
  3) Provider diagnosis
     - Diagnosed by health care provider
     - Does not fulfill all criteria necessary to meet laboratory or clinical case definitions

ADDITIONAL SURVEILLANCE INFORMATION

- Epi link to another verified case
- Mode of identification:
  - contact investigation,
  - targeted testing for TB infection,
  - evaluation of clinical signs/symptoms,
  - incidental finding
- Country of birth
- Country of birth for parent/guardian
- h/o living abroad

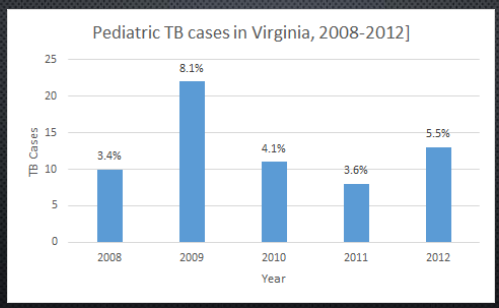
US STATISTICS: 2012

- 9,945 TB total cases were reported among all age groups
  - **486** (4.9%) were children <15 years

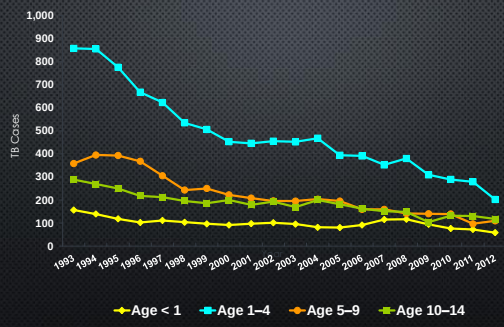
Age Group (yrs)	N	% of pediatric cases	% of total US cases
0-4	260	53.5%	2.6%
5-14	226	46.5%	2.3%

Adapted from CDC:
http://www.cdc.gov/tb/publications/slidesets/pediatricTB/default.htm

LOCALLY



PEDIATRIC TB CASES BY AGE GROUP, 1993–2012, N=19,840



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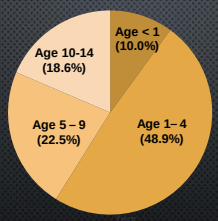

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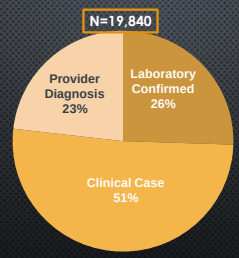
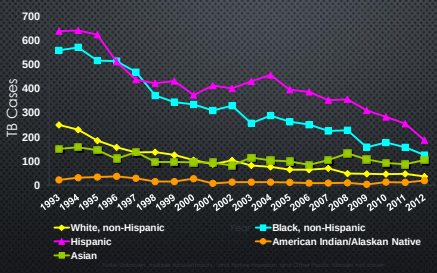
TYPE OF DIAGNOSIS: 1993-2012



RACE/ETHNICITY OF PEDIATRIC TB CASES 1993–2012, N=19,840



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Pediatric and Adolescent Tuberculosis in the United States, 2008–2010

PEDIATRICS Volume 130, Number 6, December 2012

AUTHORS: Carla A. Winston, PhD, MA and Heather J. Menzies, MD, MPH

- N=2660 (7%)
- 69% were US born (avg age: 5.5 yrs),
  - Majority of Hispanic origin
  - 66% had 1 foreign-born parent
  - 25% had no known international contact

Pediatric and Adolescent Tuberculosis in the United States, 2008–2010

PEDIATRICS Volume 130, Number 6, December 2012

AUTHORS: Carla A. Winston, PhD, MA and Heather J. Menzies, MD, MPH

- 31% foreign born (avg: 11 yrs) from:
  - Mexico (19%),
  - Philippines (9%),
  - Ethiopian (6%)
  - Haiti (6%),
  - Burma (5%),
  - Somalia (5%)
  - Vietnam, China + India (4% each)
- 11% INH-resistant, 4% MDR-TB.

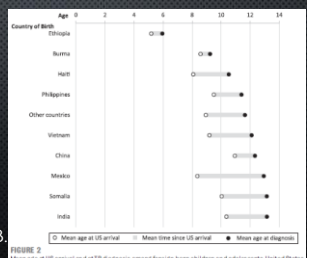


FIGURE 2
Mean age at US arrival and at TB diagnosis among foreign-born children and adolescents, United States, 2008–2010.

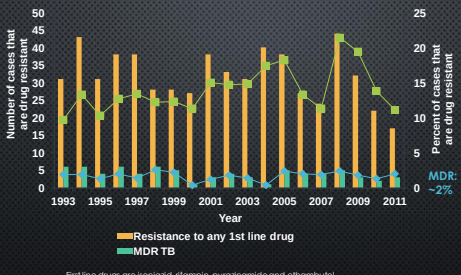
Pediatric and Adolescent Tuberculosis in the United States, 2008–2010

PEDIATRICS Volume 130, Number 6, December 2012

AUTHORS: Carla A. Winston, PhD, MA and Heather J. Menzies, MD, MPH

- Drug resistance
  - US born: 6% INH-resistant, 1% MDR-TB
  - Foreign born: 11% INH-resistant, 4% MDR-TB.

CULTURE-CONFIRMED PEDIATRIC TB CASES WITH DRUG RESISTANCE, 1993–2011



First line drugs are isoniazid, rifampin, pyrazinamide and ethambutol
MDR TB = resistance to at least isoniazid and rifampin

Multidrug-resistant tuberculosis in children: evidence from global surveillance

Matteo Zignol[1], Charalambos Sismanidis[1], Dennis Falzon[1], Philippe Glaziou[1], Masoud Dara[2] and Katherine Floyd[1]

Eur Respir J 2013; 42: 701–707

- 2000-2011
- N= 323,046 cultures
  - 6,070 from children (2%)
- No association between MDR TB and age

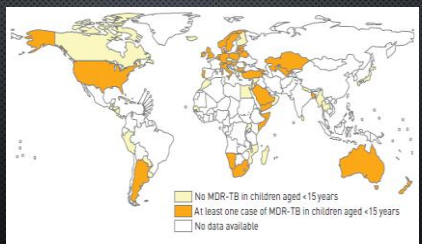


FIGURE 1 Countries that reported drug resistance survey/surveillance data disaggregated by age group, 2000–2011. MDR-TB: multidrug-resistant tuberculosis.

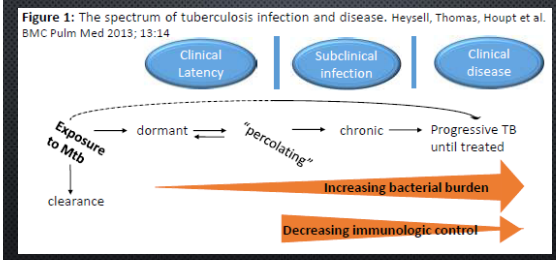
TO RECAP: EPIDEMIOLOGY & HIGH RISK GROUPS:

- Children comprise about 5% of TB cases in the US
- Young children, esp <5 years, are at high risk of developing TB disease
- Children with foreign roots (not just foreign born) are at higher risk of having TB disease
  - Hispanic roots > SE Asia, Africa and Caribbean
  - Not limited to new immigrants
- Children can have drug resistant TB
  - Foreign born children have higher rates of drug resistance

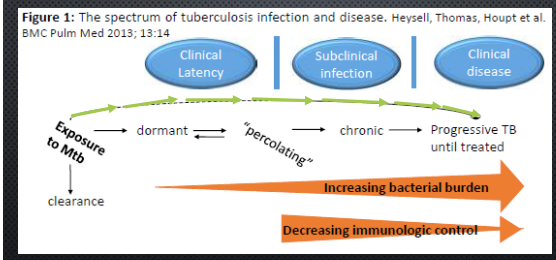
THE SPECTRUM OF TB:

LATENT INFECTION TO ACTIVE DISEASE

SPECTRUM OF DISEASE



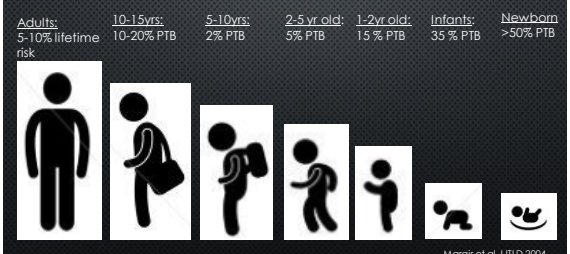
SPECTRUM OF *PEDIATRIC* DISEASE



- Rapid progression to TB disease
- Greater risk of disseminated disease

IMMATURE IMMUNE SYSTEMS:

- Rapid progression from exposure to disease



Marais et al. IJTLD 2004
Peng et al. Ped Pulm. 2011

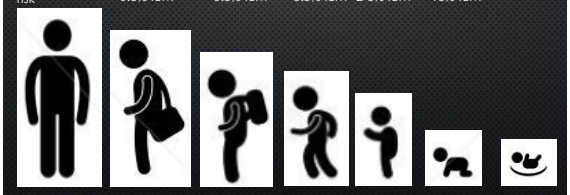
RISK FACTORS FOR DISEASE PROGRESSION

- Younger age
- Higher inoculum of exposure
- Malnutrition
- HIV co-infection
- Otherwise weakened immune system
- Virulence of the TB strain

IMMATURE IMMUNE SYSTEMS:

- Rapid progression from exposure to disease
- Higher proportion of extra-pulmonary disease

Adults:	10-15yrs:	5-10yrs:	2-5 yr old:	1-2yr old:	Infants:	Newborn
5-10% lifetime risk	10-20% PTB <0.5% TBM	25% PTB <0.5% TBM	35% PTB <0.5% TBM	15-35% PTB 2-5% TBM	35 % PTB 15% TBM	>50% PTB 10% TBM?



Marais et al. IJTLD 2004
Peng et al. Ped Pulm. 2011

SITES OF DISEASE

- Intra-thoracic disease: 60-80%
  - Disease in the lung tissues
  - Disease in the intrathoracic lymph nodes
- Remainder is Extrapulmonary
  - Lymphadenopathy, 67%
  - Central Nervous System, 13%
  - Pleural, 6%
  - Disseminated/Miliary, 5%
  - Skeletal, 4%
  - Other sites, 5%

SPECTRUM OF SIGNS AND SYMPTOMS

WHAT TOOLS DO WE USE?

- Tuberculin Skin Test/IGRA
- Symptoms & History
- Chest X-ray
  - Two views are ideal
- Smear/Culture,
- GeneXpert
- Score Card

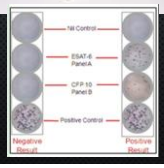
TB EXPOSURE STATUS:

- Check the TST via the Mantoux method

READING & INTERPRETING THE TST

- Measure induration after 48-72 hours
- ≥5 mm :
  - Immunocompromised: HIV
  - Close contacts of infectious cases
  - Children with CXR showing fibrotic changes consistent with old TB
- ≥10 mm:
  - Recent arrivals from high-prevalent countries
  - Condition that increases risk of progression to disease: malnutrition
  - Children < 4yrs
- ≥15 mm:
  - Healthy children >4 years with no known risk factors

INTERFERON GAMMA RELEASE ASSAYS



SELECTING A TEST TO DETERMINE TB EXPOSURE STATUS

- IGRAs ARE PREFERRED METHOD OF TESTING FOR
  - Groups of people who have poor rates of returning to have TST read
  - Persons who have received BCG vaccination
- TST IS THE PREFERRED METHOD OF TESTING FOR
  - Children under the age of 5 years

IF TST/IGRA IS NEGATIVE:

- In contact investigations, confirm a negative test via retest
  - 8-10 weeks post-exposure
  - Use the same test for repeat testing to reduce misclassification errors

IF A TST/IGRA IS POSITIVE

- DETERMINE IF CHILD HAS "TB" OR "LTBI"
- TB: child has an active infection from *M. tuberculosis* bacteria in some part of the body
  - May have subtle symptoms or only radiographic changes
- LTBI: child has been exposed to the *M. tuberculosis* bacteria but immune system is controlling infection in a "dormant" state.
  - Physical exam and X-rays are normal

TST RESULTS ARE NOT DEFINITIVE

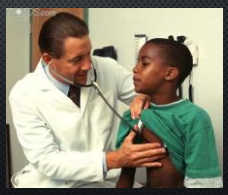
- A POSITIVE TST DOES NOT CONFIRM THE DIAGNOSIS OF TB DISEASE
- A NEGATIVE TST DOES NOT EXCLUDE TB
- TST RESULTS ARE MERELY ONE ASPECT OF THE EVALUATION.

FOCUSED HISTORY:

- Symptoms are more obvious in infants and young children
- School aged children may have no symptoms (but + CXR)
- TB CONTACTS, COUGHING CONTACTS?
- Pulmonary TB:
  - Chronic cough (>3 weeks)
  - Fever (>38' for 2 weeks+)
  - Weight loss or failure to gain weight
- Extra-pulmonary TB:
  - TB adenitis: Painless, enlarged lymph nodes, esp in the neck region
  - Meningitis (not responsive to typical antibiotics)
  - Abdominal TB: distended abdomen, ascites
  - Can also involve the joints, bones, skin, kidneys, eyes

FOCUSED PHYSICAL EXAM

- Temperature and growth parameters
- Level of alertness
- Lung Exam*
- Peripheral lymph nodes
- Abdominal exam
- Palpate back and extremities
- Signs of meningitis



PHYSICAL EXAM: LUNG EXAM

- Can be normal
  - even if chest X-ray is NOT
- Increased work of breathing, decreased breath sounds and crackles are most common among infants and adolescents.

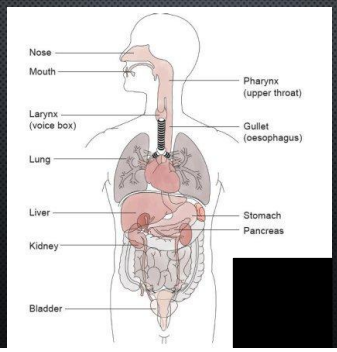
CHEST RADIOGRAPH

- Two views (frontal & lateral) are recommended
  - Helps identify lymph node enlargement
- Discuss suspicion for TB with radiologists

OBTAINING SPECIMENS MAY BE DIFFICULT

- Not able to cough on command
  - Invasive procedures required to get a specimen
  - Requires time and skill
  - Uncomfortable for the child
- Higher proportion of extrapulmonary disease
  - Invasive procedures required to get a specimen
  - May need referral to specialists

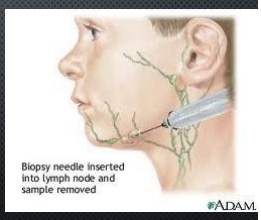
WHAT KIND OF SPECIMENS CAN WE COLLECT FOR SUSPECTED PULMONARY TB?



WHAT KIND OF SPECIMENS CAN WE COLLECT FOR LYMPH NODE DISEASE?

- Aspirate of pus from inside lymph node(s)
- Biopsy of lymph node
- Excision of lymph node

- Is the child coughing?
  - May collect respiratory specimen



LESS LIKELY TO HAVE POSITIVE AFB OR CULTURE

- WHY?
- TB AFFECTS CHILDREN DIFFERENTLY THAN ADULTS
  - "PAUCIBACILLARY" DISEASE: FEWER TB BACILLI IN SPECIMENS
  - SYMPTOMS MAY NOT BE AS PRONOUNCED.

CULTURE YIELD

- BRONCHO-ALVEOLAR LAVAGE:
  - 4-43% YIELD
- GASTRIC LAVAGE:
  - 10-90% YIELD → USUALLY ~30%
- SPUTUM INDUCTION/NASOPHARYNGEAL ASPIRATION:
  - 20-30%
- LYMPH NODE
  - 38-70%, PCR 70%
- CULTURE IN LIQUID MEDIA SUPERIOR TO SOLID AGAR
- **A NEGATIVE TEST DOESN'T RULE OUT TB DISEASE**

Swaminathan & Rekha, *CID*, 2010
van Wyk et al, *IJTLD*, 2010

MOLECULAR TESTS: GENEXPERT MTB/RIF

- NOT YET FDA APPROVED FOR USE IN CHILDREN
- USED AROUND THE WORLD WITH IMPROVED SENSITIVITY COMPARED TO AFB SMEAR IN CHILDREN

TO RECAP: SPECTRUM OF TB IN CHILDREN

LATENT TB INFECTION

- TST/IGRA POSITIVE
- CHEST X-RAY IS NORMAL
- NO SIGNS/SYMPTOMS SUGGESTIVE OF TB
- SPECIMENS ARE SMEAR/CULTURE NEGATIVE (IF DONE)

TB DISEASE

- TST/IGRA USUALLY POSITIVE
- CHEST X-RAY USUALLY ABNORMAL (IF PULMONARY TB)
- SYMPTOMS PRESENT
- MAY BE CULTURE POSITIVE
  - AND/OR SMEAR/PCR POSITIVE

TO RECAP: SPECTRUM OF TB IN CHILDREN

- YOUNG CHILDREN CAN RAPIDLY PROGRESS TO DISEASE AFTER EXPOSURE
- TB CAN AFFECT ANY PART OF THE BODY
- A NORMAL CLINICAL EXAMINATION DOES NOT RULE OUT INFECTION
- CHEST X-RAYS ARE A VERY USEFUL TOOL
- DIAGNOSTIC TESTS ARE NOT 100% ACCURATE IN CHILDREN
- MAINTAIN A HIGH LEVEL OF SUSPICION FOR TB DISEASE

TREATMENT OPTIONS

TREATMENT OF TB DISEASE

Disease category	Intensive phase (2 months)	Continuation phase
New patient Sputum smear negative Pulmonary TB	INH/ RIF/ EMB*	INH/ RIF→ 4 months
Cervical adenitis	INH/ RIF/ EMB/ PZA	INH/ RIF→ 4 months
TB meningitis	INH/ RIF/ EMB/ PZA	INH/ RIF → 10 months
Osteoarticular	INH/ RIF/ EMB/ PZA	INH/ RIF → 10 months

LTBI REGIMENS:

Drug(s)	Duration	Interval	Min Doses	Within
Isoniazid	9 months	Daily	270	12 months
		Twice weekly	76	
	6 months	Daily	180	9 months
		Twice weekly	52	
Isoniazid & Rifapentine	3 months (≥12 yrs of age)*	Once weekly	12	4 months
Rifampin	4 mo (adults)*	Daily	120	6 months
	6 mo (children)		180	

Journal of the Pediatric Infectious Diseases Society Advance Access published January 16, 2014

Original Article

Rifapentine Pharmacokinetics and Tolerability in Children and Adults Treated Once Weekly With Rifapentine and Isoniazid for Latent Tuberculosis Infection

Marc Weiner,[1,2,a] Radojka M. Savic,[1,a] William R. MacKenzie,[3] Diane Wing,[3] Charles A. Peloquin,[4] Melissa Engle,[1] Erin Bliven,[5] Thomas J. Priboda,[6] Jonathan A. L. Gelfond,[7] Nigel A. Scott,[8] Susan M. Abdel-Rahman,[9] Gregory L. Kearns,[9] William J. Burman,[3] Timothy R. Sterling,[10] and M. Elsa Villarino[3]; for the Tuberculosis Trials Consortium PREVENT TB Pharmacokinetic Group

- 80 children (ages 2-11 years)
- Dose for children 2-fold higher compared to adults
- Achieved 1.3-fold higher drug-level concentration
- Well tolerated
- Associated with successful treatment outcomes

Table 1. Rifapentine Dosing for Children With Latent Tuberculosis Infection in the Present Study[a]

Weight (kg)	Rifapentine Dose (mg)	Rifapentine Dose (mg/kg)	Age of Study Patients, y (mean ± standard deviation)
10–14	300	21–30	2.6 ± 0.8
>14–25	450	18–32	4.5 ± 1.6
>25–32	600	19–24	7.4 ± 2.2
>32–50	750	15–23	9.7 ± 2.4
>50	900	<18	38.8 ± 12.9

[a] N = 80 children. Same dosing guideline was used for children in the PREVENT TB trial.

Safety and completion of a 4-month course of rifampicin for latent tuberculous infection in children

A. T. Cruz,*† J. R. Starke*

Among 404 children with LTBI

- 4 RMP (20%) vs 9 INH (80%)
- 50% DOPT, 50% self-completion

RESULTS:

- Improved self-completion
- Well tolerated

QUESTIONS?

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